Potency of Poxviral Based Vectors for Malaria and TB vaccines

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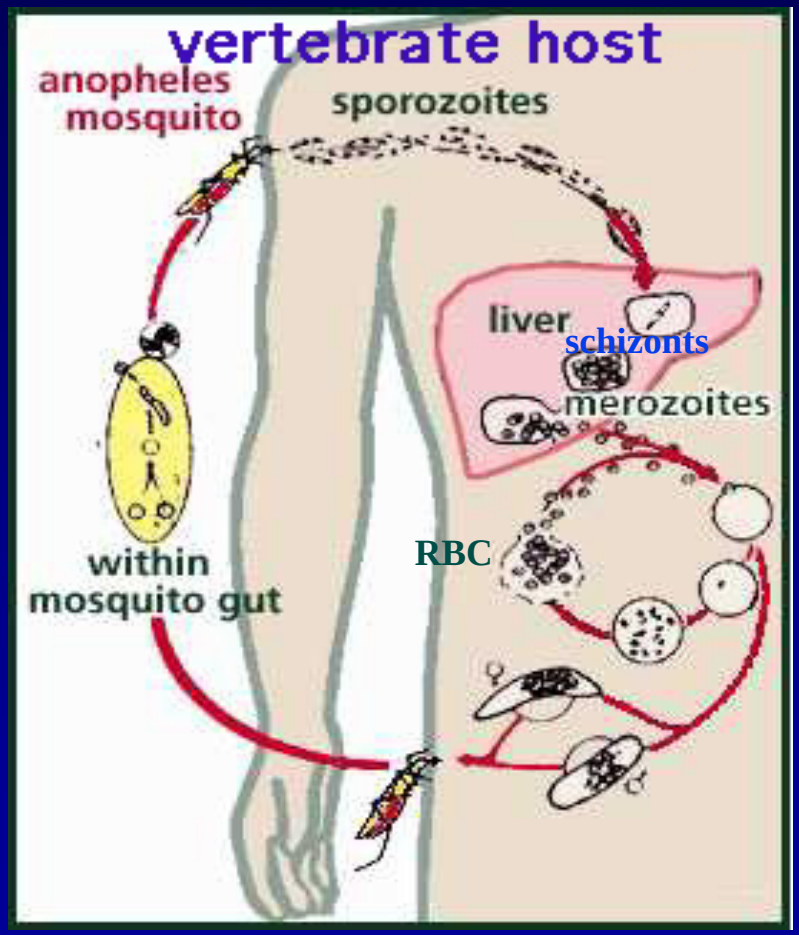
Malaria Vaccines in Clinical Development

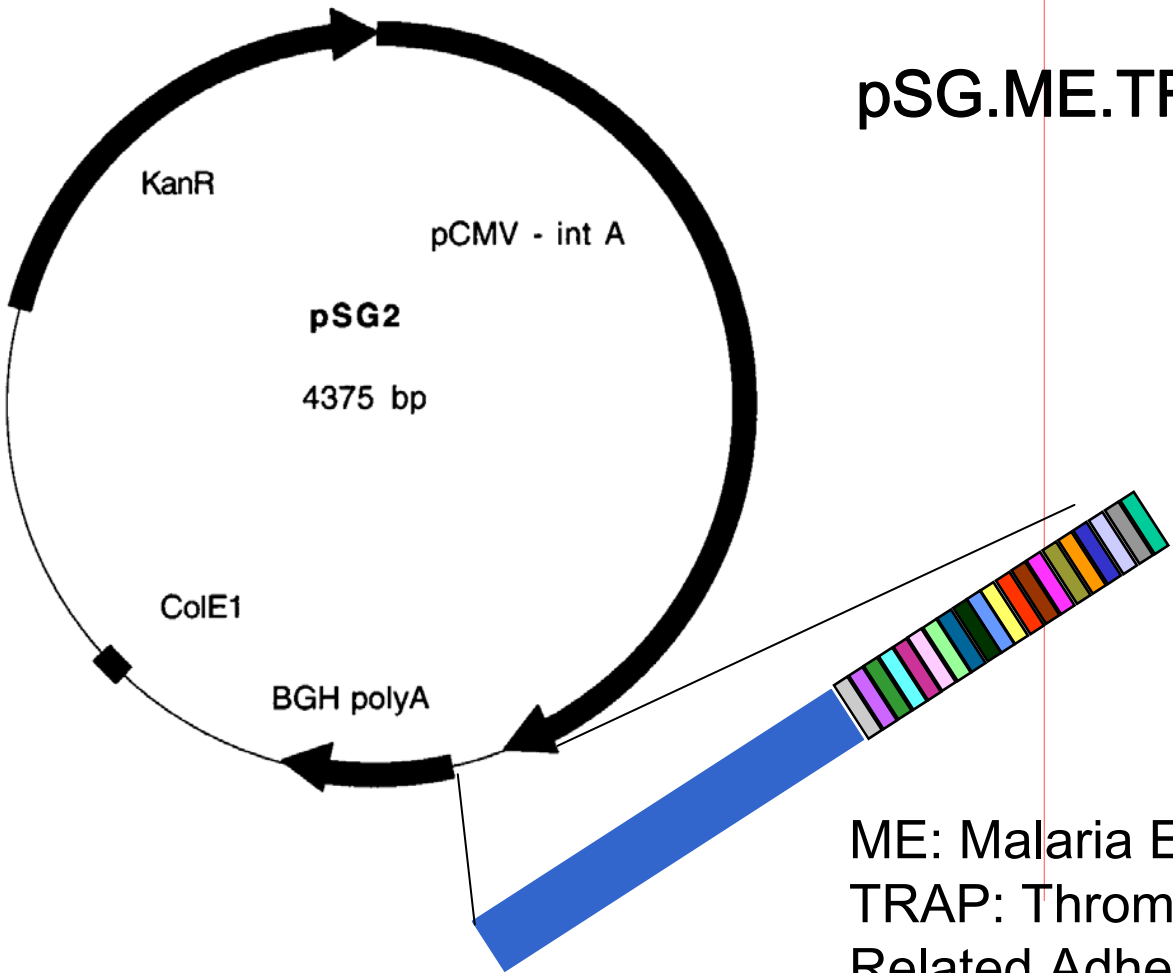


Pre-erythrocytic Strategies

- Prevent sporozoite invasion of liver cell: Antibody

- Prevent sporozoite surviving, replicating in and progressing from liver cell:
  T cell

Recombinant Malaria Vaccines

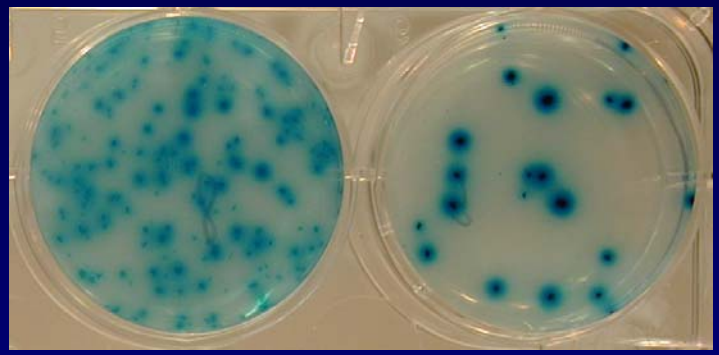


pSG.ME.TRAP

ME: Malaria Epitopes
TRAP: Thrombospondin-Related Adhesion Protein

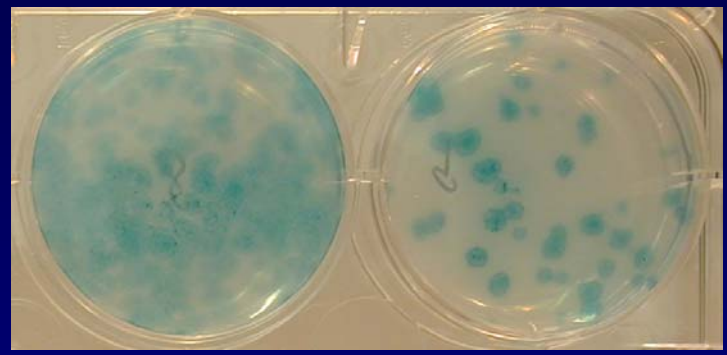
CSO construct: codon optimised *Pf*CS, with C-term Pb9 (PbCSP epitope)

Recombinant Poxviruses



MVA

- Highly attenuated vaccinia virus strain
- Deletions in host range genes and cytokine genes
- Replicates in chick embryo fibroblasts but not in mammalian cells
- Excellent safety record - over 120,000 people immunised with MVA

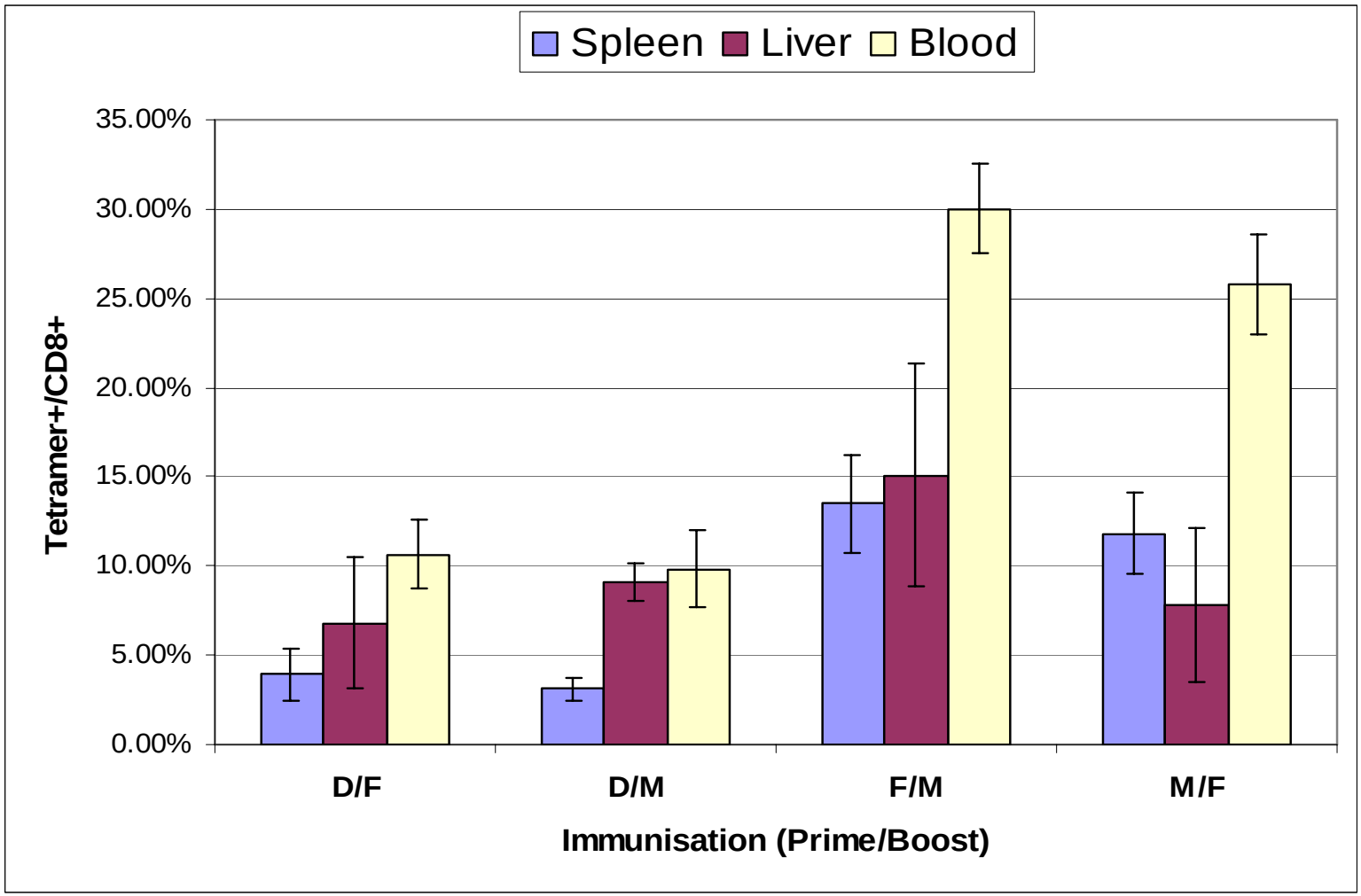


Fowlpox9

- An avipoxvirus, like canarypox
- Attenuated by Anton Mayr (Munich)
- Characterised molecularly by the Institute of Animal Health, Compton, UK (Mike Skinner)
- Shown in Oxford to be more immunogenic for CD8+ T cell induction than the standard fowlpox strain

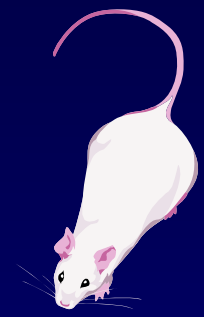
Malaria Vaccines in Mice

Pb9-specific CD8+ T-cells in Spleen, Liver and Blood



Anderson et al J.I. 2004

Protective efficacy of prime-boost immunisation regimes



Prime / Boost	Animals Protected	Efficacy (%)
FP / MVA	**27 / 40**	**67.5**
MVA / FP	**15 / 40**	**37.5**
FP /FP	3 / 19	15.7
MVA / MVA	3 /20	15.0

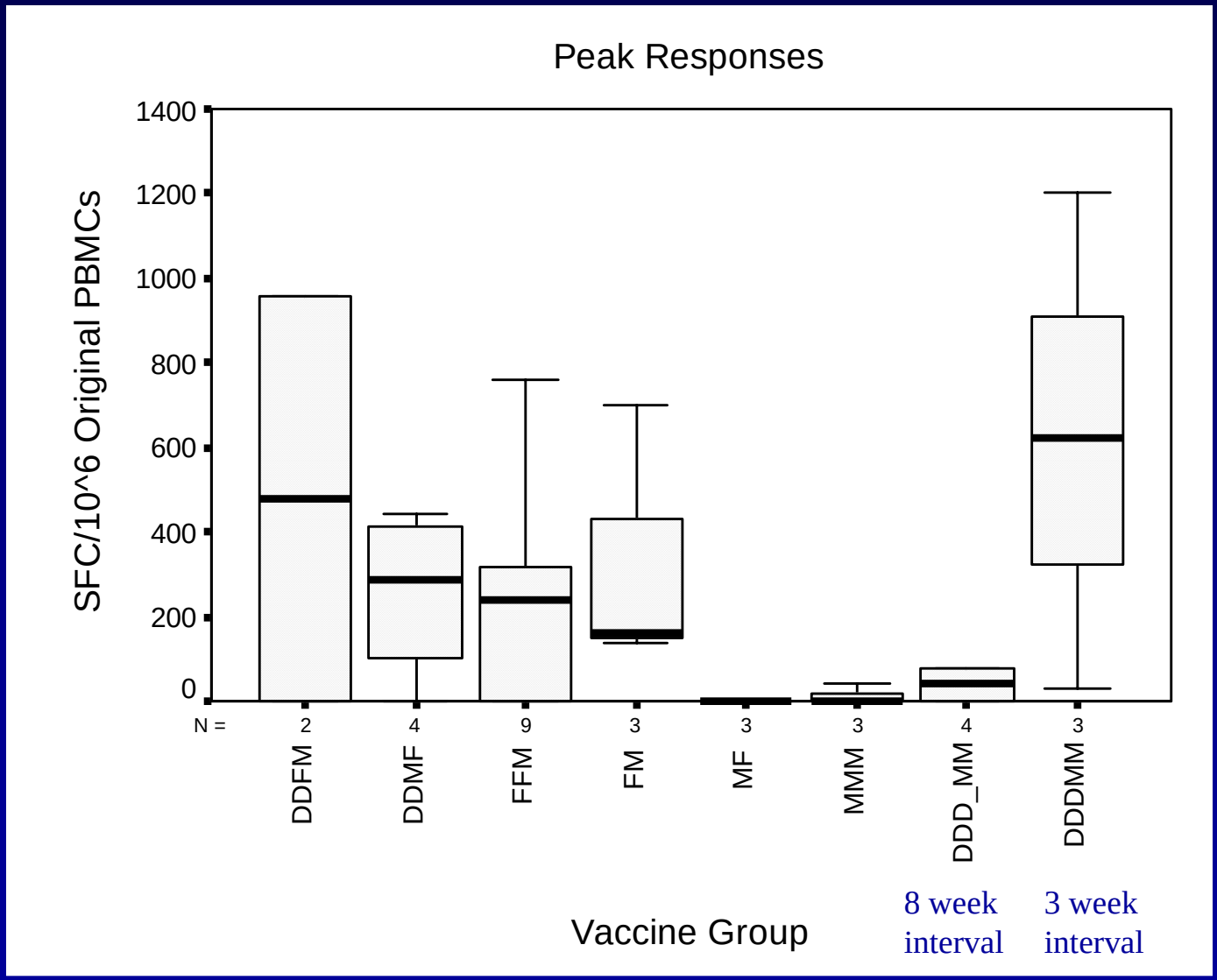
2000 sporozoites

Anderson et al J.I. 2004

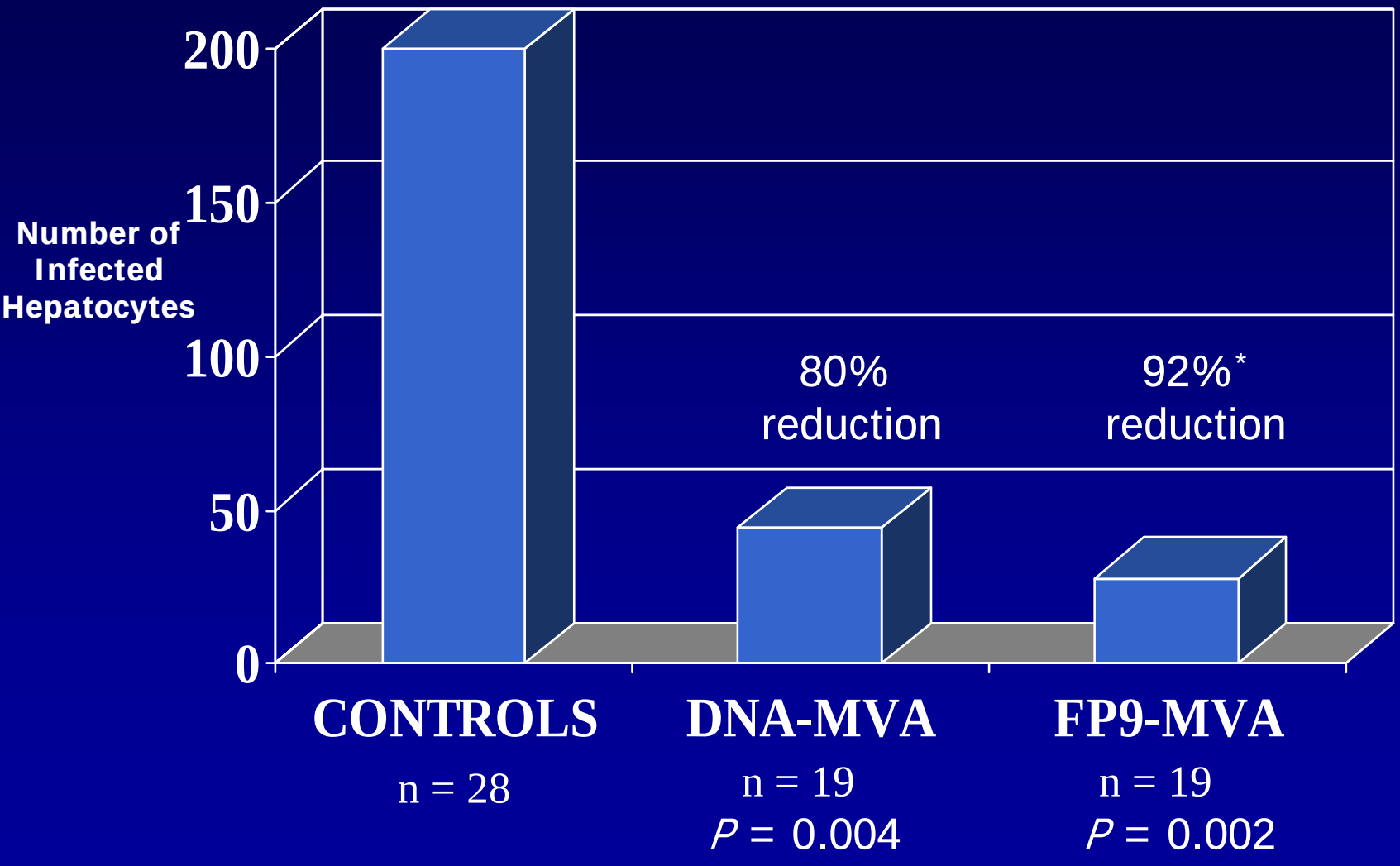
Oxford University Malaria Vaccine Trials

		Vaccinees	Challengees	Year
VAC 01	DNA im vs gene gun +/- MVA boost id	12		1999
VAC 02	MVA id	6		
VAC 03	DDDM, DMM, DDD, MMM	15		
VAC 04	challenge study for 03		17	
VAC 05	DDMM vs GGMM	9		2000
VAC 06	*Gambia: DDMM vs MMM*	*18*		
VAC 07	challenge study for 05		14	
VAC 08	MVA boosting of sporozoite challengees	4		
VAC 09	MVA higher dosages	6		2001
VAC 10	DDMM higher dose, longer interval	9		
VAC 11	*Gambia: 1-5 year old children MVA*	*20*		
VAC 12	FP9 phase I and high dose MVA boost	12		
VAC 13	challenge studies for 10 and 12		14 + 10	
VAC 14	*Gambia: FFM, DDM, DDDM high dose*	*30*		
VAC 15	FFM vs MMM high dose	17		2002
VAC 16	challenge study for 15		22	
VAC 17	FM, MF, DDFM, DDMF	17	23	
VAC 18	RTS,S MVA-CS, MVA-CS RTS,S	24	17	
VAC 19	*Kilifi, Kenya FM, FFM*	*30*		
VAC 20	*Gambia DDM vs rabies*	*328*		

Immunogenicity in Man: *Ex Vivo* Elispot Responses; Oxford-based trials



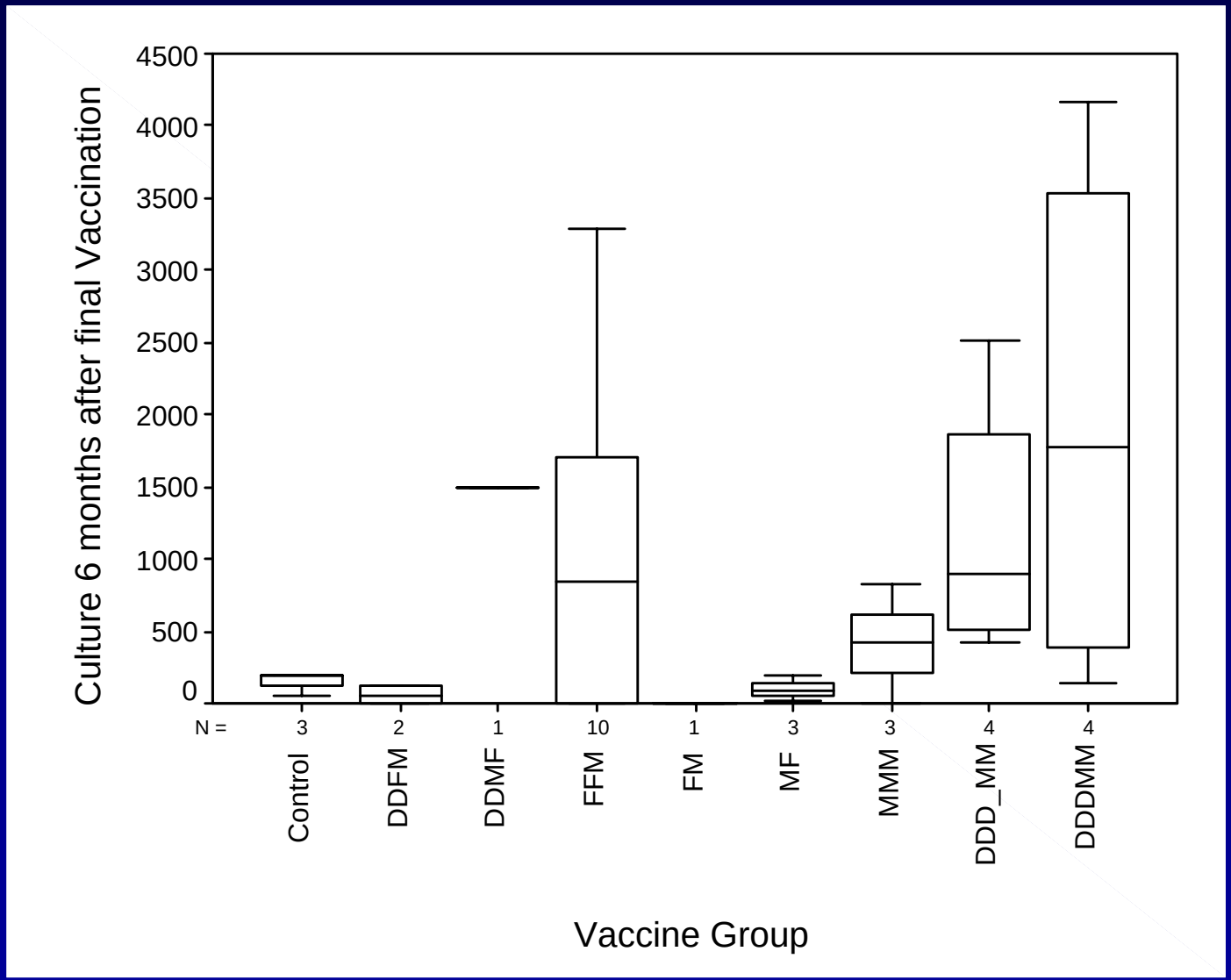
Malaria Vaccine Efficacy
in Oxford Sporozoite Challenge Studies



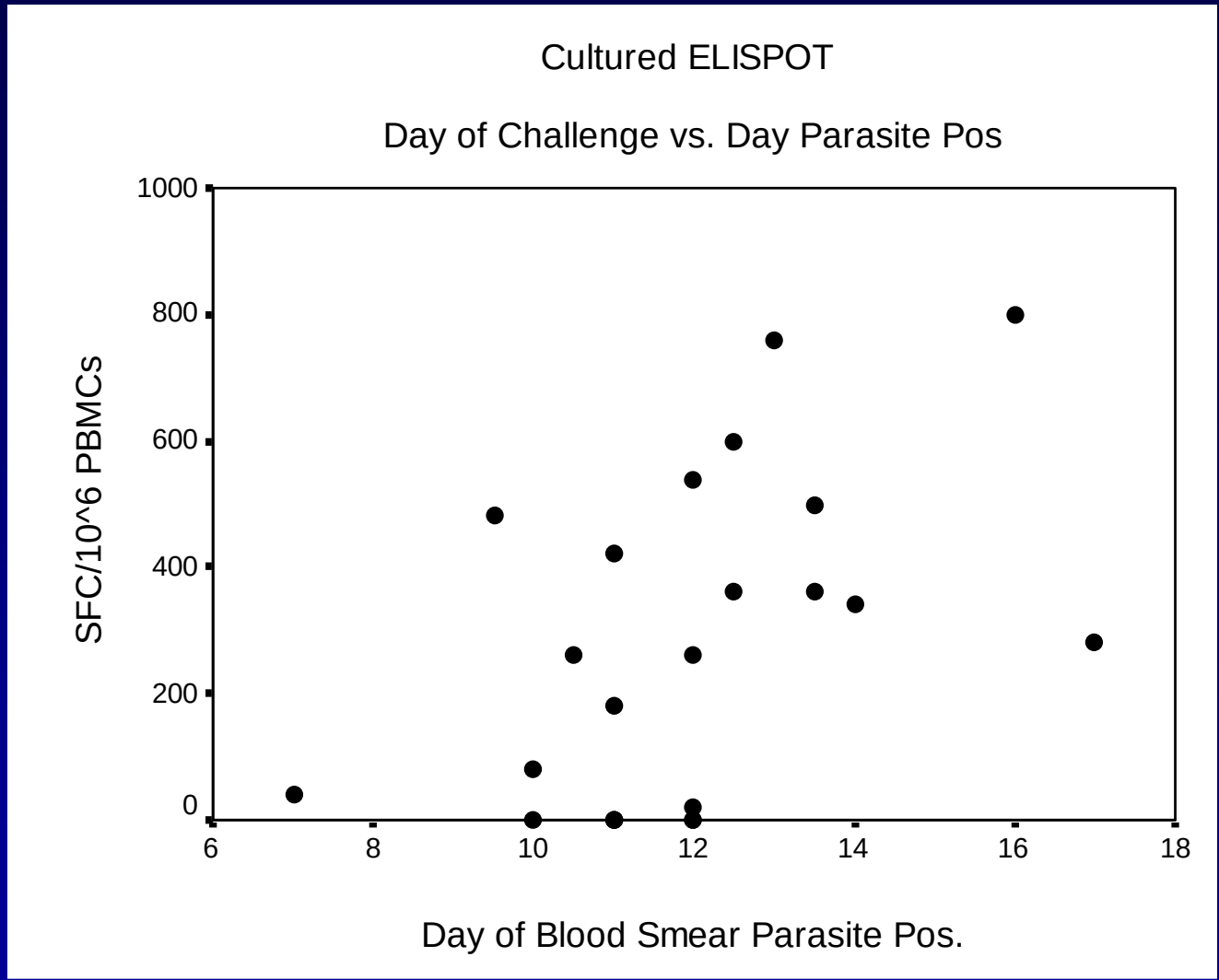
All vaccines express ME-TRAP

*Bejon et al. *J. Infect. Dis.* (2004)

Cultured ELISPOT Responses



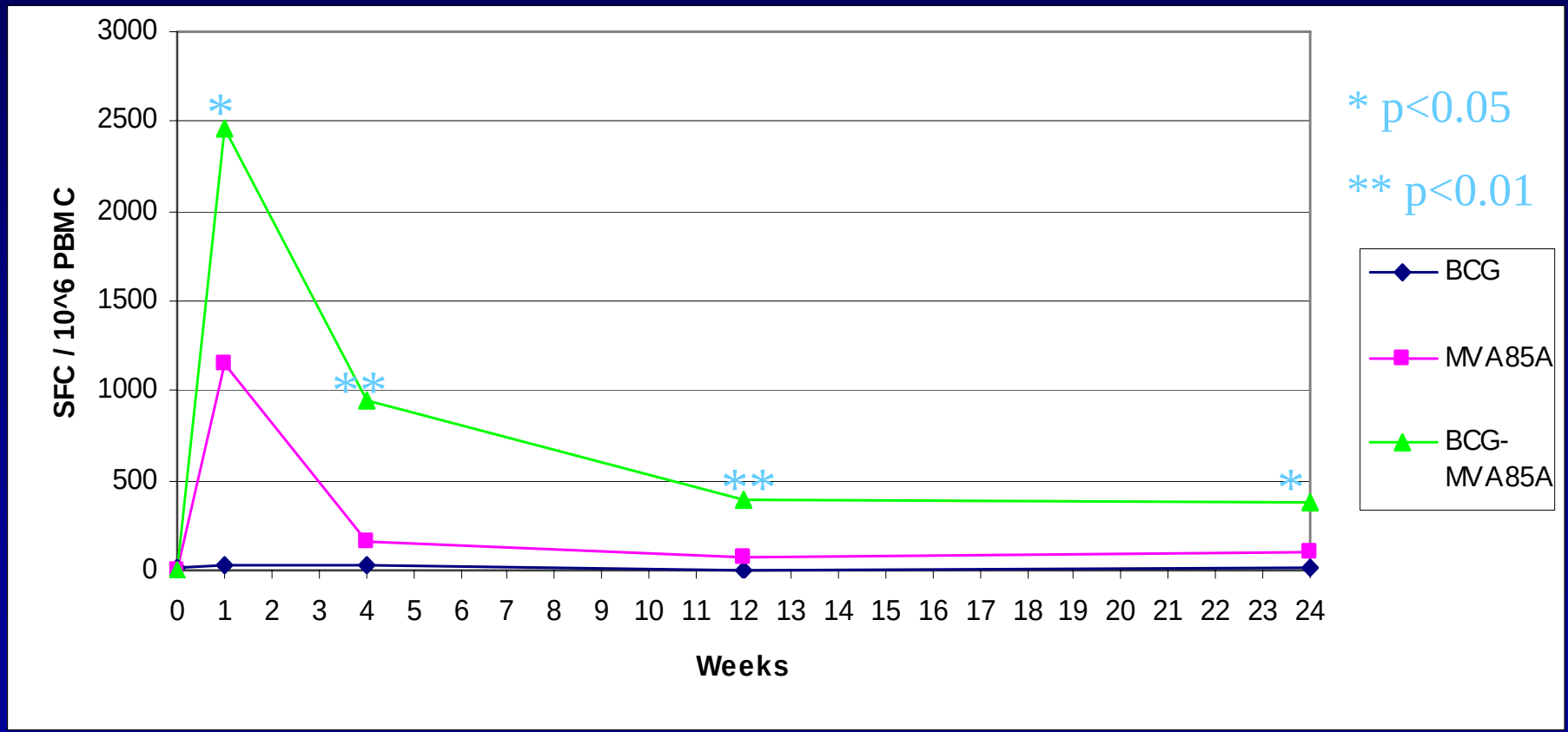
Correlation with Delay to Parasitemia



Spearman r= 0.499; p=0.015

TB trials

Median Elispot summed peptide pool responses: BCG v MVA85A v BCG-MVA85A



McShane et al, Nature Medicine, 2004

Conclusions from Vaccine Studies

- Heterologous prime-boost regimes that work in mice also work in humans. Murine model can predict vaccine efficacy.

- Correlates of immunity? Malaria: Memory T cell responses (cultured elispot at day of challenge) strongly correlate with delay to parasitemia. TB: CD4+ T cell responses?

Phase I & IIa/b Clinical Vaccine Production & Release

Oxford: - Candidate Recombinant Poxvirus Vaccine:
- Confirm insert sequence, identity & purity PCR (absence of WT virus)
- Confirm immunogenicity: Potency assay in mice (IFN-γ elispot)

IDT, Germany - GMP manufacture of clinical lot:
- QA/QC: Purity,
Viral Titre, live infectious virus
Lack of Extraneous agents, Endotoxin, Mycoplasma
Lack of Replication Competence

HLS - Toxicology
- Persistence & distribution

Oxford: -QA/QC:
Purity, Insert Sequence,
Viral Titre,
Immunogenicity; Potency assay

Batch released for clinical use.

Potency Assay: IFN-γ ELISPOT Assay

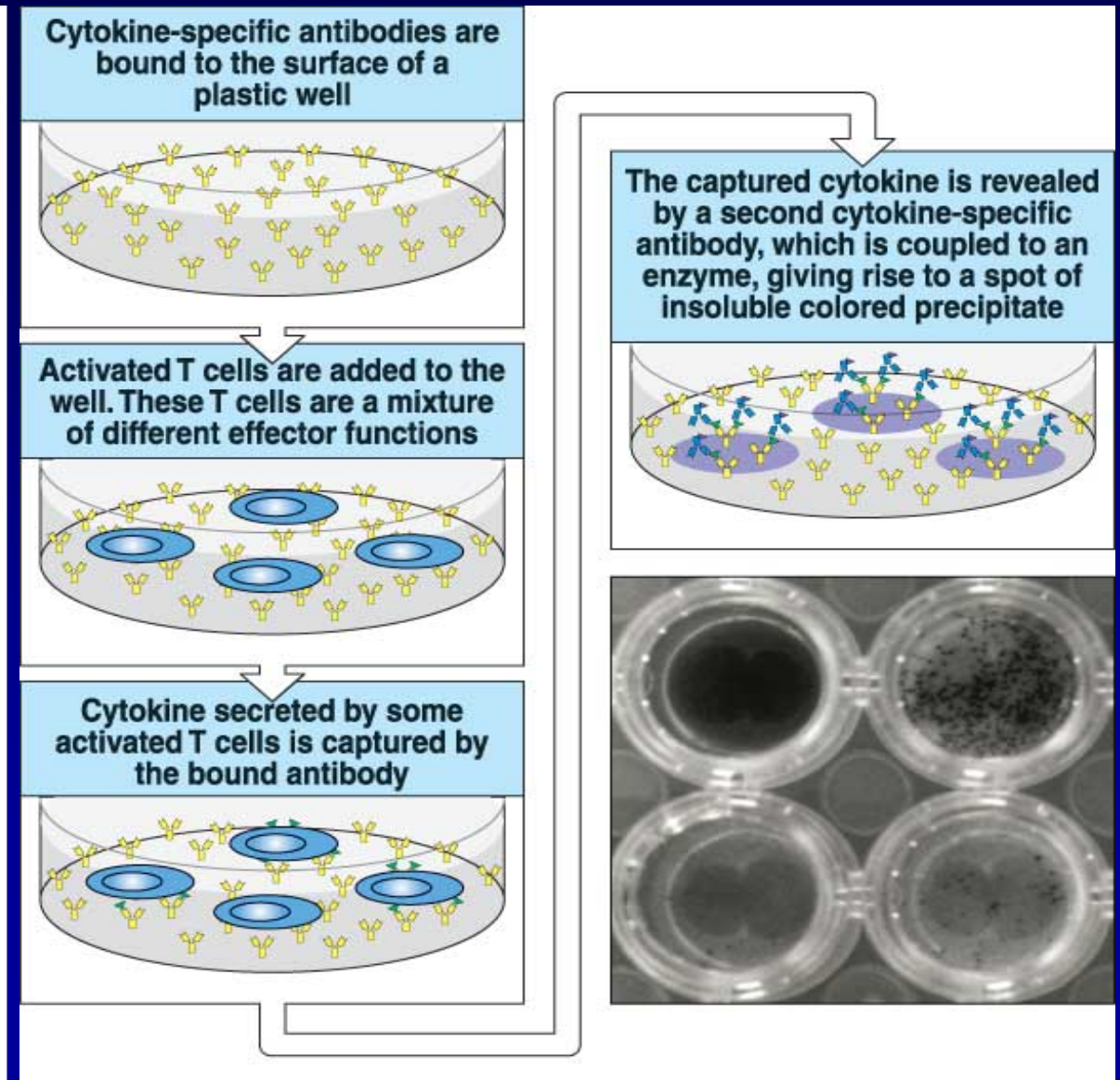
4 mice immunized, Antigen-specific response > 15sfc/million, no more than 1 non-responder

Antigens tested

***P. berghei* MHC class I Peptide; Pb9 SYIPSAEKI**

OR

***M.tb*85A MHC class I & II epitope**



Phase III & Beyond…

- Dose titration potency assay; increase sensitivity; detect subtle differences between lots
- 3Rs; should move away from routine potency testing in animals
- Alternative: does *in vitro* mRNA or protein expression correlate with immunogenicity *in vivo?*
- Tests to quantify the protein expression to be implemented

Future Directions in Production & Validation of Recombinant Virus Vector-based Vaccines

- New antigens or combinations of expressed antigens; Polyprotein construct; new challenges with larger inserts.
- New viral vectors; Adenoviruses
- New GMP facilities; Oxford GMP facility to produce clinical lots of recombinant ADV-METRAP & poxvirus-based vaccines.

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